INSTITUTE OF PUBLIC HEALTH

COLLEGE OF MEDICINE AND HEALTH SCIENCE

UNIVERSITY OF GONDAR

Rate of Immunological Failure and Its Predictors among Patients on Highly Active Antiretroviral Therapy at Debremarkos Hospital, Northwest Ethiopia

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Examiner

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My deepest thankfulness will also goes to my friends especially to G/Selassie Demeke for logistic support and providing constructive comments for the betterment of this research report.

My grandmother, *Emahoy* Zewditu Tegegne, deserves my wholehearted appreciation for teaching me to be me.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
AHR	Adjusted Hazard Ratio
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral Drug
AZT	Zidovudine
d4t	Stavudine
DDI	Didanosine
E.C	Ethiopian Calendar
EFV	Efavirenz
G.C	Gregorian Calendar
HAART	Highly Active Anti- Retroviral Therapy
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IQR	Inter Quartile Range
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside analogue Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
TLC	Total Lymphocyte Count
UNAIDS	United Nations' Program on HIV/AIDS
URTIs	Upper Respiratory Tract Infections
VL	Viral Load
WHO	World Health Organization

ABSTRACT

Introduction: Since the mid-1990s, antiretroviral drugs have been effective in prolonging the life span of people infected with HIV. Viral load monitoring is the gold standard to diagnose failure of antiretroviral treatment but it is not generally available in resource-limited settings. Thus in resource-limited settings patients on antiretroviral treatment monitored by using immunological and clinical follow up, this keep patients on a failing regimen.

Objective: To determine the rate and associated factors of Immunological failure among patients on highly active antiretroviral treatment (HAART) at Debremarkos hospital, Northwest Ethiopia, May 2012.

Methods: Retrospective longitudinal study was conducted on 509 adults who started HAART at Debremarkos hospital within a period of January 01, 2007 to April 01, 2008. Medical records of these patients were reviewed from ART start date up to April 01, 2012. The data were collected from clients ART chart using data extraction format by trained nurses. Data were entered in to Epi-Info 2002 and exported into SPSS windows version 20 for analysis. Kaplan-Meier curve was used to estimate the time to event. Both bivariate and multivariate Cox proportional hazards models were used to identify predictors of immunological failure.

Result: The median age at initiation of treatment was 35 (IQR: 11) years and the median follow up time was 36 months (IQR=37 months). Among study participants 302 (59.3%) were females. At the end of follow up, 107(21%) had developed immunological failure. The rate of immunological failure after 63 months on ART was 8 per 100 patient-years. Recurrent pneumonia infection (AHR=1.623, 95%CI: 1.095, 2.404), unemployment (AHR: 1.741, 95%CI: 1.107, 2.738), baseline CD4 count ≤100 cells/mm^3 (AHR: 2.160, 95%CI: 1.435, 3.252) and No change or decrease in body weight (AHR: 4.335, 95%CI: 2.930, 3.229) were significant predictors of immunological failure.

Conclusion and Recommendations: The immunological failure rate was higher than other sub-Saharan Africa studies. It will be good to monitor patients who had higher risk of immunological failure with viral load monitoring not to let them on failing regimen.

Key Words: Antiretroviral therapy, Immunological failure, Survival analysis

1. INTRODUCTION

1.1. STATEMENT OF THE PROBLEM

According to World Health Organization (WHO) statistics, globally there were about 34.0 million people living with HIV in 2010 (1). Sub-Saharan Africa continues to bear an inordinate share of the global HIV burden there were about 23 million people living with HIV/AIDS in the region (2). Ethiopia belongs to the heavily affected countries of Sub-Saharan Africa by HIV/AIDS, at a prevalence rate of 2.4%, an estimated of 1,216,908 people living with HIV/AIDS in 2010 (3).

Since the mid-1990s, antiretroviral drugs have been effective in prolonging the life span of people infected with HIV, transforming HIV from a fatal acute disease to a manageable chronic condition (4). According to Federal HIV/AIDS Prevention and Control Office at the beginning of February, 2010 Cumulative number of people ever started antiretroviral treatment (ART) in Ethiopia were 246,347 among these 232697 were age >14 years (5).

Although, the primary goal of highly active antiretroviral treatment (HAART) is to suppress viral load below the level of detection within three to six months of starting therapy and to maintain it for the rest of the patient's life, there are also other important goals of HAART including restoring and preserving immunologic function, reducing HIV-related morbidity and mortality, improving quality of life and reducing vertical transmission (6).

One challenge to antiretroviral treatment is the requirement of consistent use of the medication in order to reduce the possibility that the virus will adapt and become resistant to the drug. Finding feasible and affordable means for early detection of treatment failure is crucial to sustain first-line therapy effectiveness (4, 7). Viral load monitoring is the gold standard used in high-income countries to diagnose failure of ART, but it is not generally available in resource-limited settings because of its expensiveness (8).

Therefore, taking resource constraints into account, and that virological failures precede immunological failures, then comes clinical failure, WHO guidelines recommend clinical and immunological (CD4+ count) assessments as surrogates for viral load to monitor patients on ART in resource limited settings (9). However, the sequential nature of treatment failure which is not strongly evidence based and may take years to happen (6).

Hence, diagnosing treatment failure based on the clinical or immunological criteria will lead keeping patients on a failing regimen which in turn leads to the reversal of clinical conditions of patients to the pre-treatment state, increase risk of mortality and development of drug resistant strains. It will be shocking if once drug resistant virus start transmission in the population (10, 11).

It would be best to look for ways of predicting treatment failure early. Knowing factors associated with ART failure will help to identify those at higher risk of developing failure earlier so that appropriate measures will be taken during their follow up to try and avoid development of failure. With this information, clinicians could give such patients special attention during their follow-up and the limited resources available for diagnosing treatment failure can be used for them.

1.2. LITERATURE REVIEW

1.2.1. ANTIRETROVIRAL TREATMENT FAILURE

Antiretroviral treatment failure is associated with virologic failure, immunologic failure, and/or clinical failure. Virological failure is said to be occurred when Plasma viral load above 5000 copies/ml and Immunological Failure when there is Fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value OR Persistent CD4 levels below 100 cells/mm^3**.** Clinical failure is said to be occurred when new or recurrent WHO stage 4 conditions occurred (12).

A study done in a university hospital in Thailand had found in 6 years follow up the cumulative incidence was 33.5% for immunological failure (13). However, in 33 months retrospective follow-up study in India, the cumulative incidence of treatment failure was low as 3.9% (14).

A six year retrospective follow up study conducted in South Africa where adults on ART were stratified by age at initiation found that 16.6% of patients had poor immunological response with the largest proportion being in those aged 50 years and above (11). Another retrospective cohort study in rural South Africa showed 13% prevalence of immunological failure (15), this value was slightly higher in a Tanzanian cross-sectional study which found 17.1% prevalence of immunological failure (16).

A retrospective follow up study conducted in rural Uganda shown that immunological failure was 7.9% at month 12 and 38% at month 24 (17). In 36-month follow up study in HIV-1 infected women in Côte d'Ivoire the overall probability of immunological failure was 0.08 at 12 months, 0.14 at 24 months and 0.21 at 36 month (18). A retrospective cohort study in Soweto, South Africa demonstrated an overall immunologic failure rate of 27% by month 48 (7).

A systematic review conducted in resource limited settings by WHO found that failure rate per 100 patient years of follow-up (PYFU) in Africa was 2.64 using clinical/immunological definitions of treatment failure (19).

1.2.2. **FACTORS ASSOCIATED WITH ART FAILURE**

Socio-demographic

A study conducted in rural Uganda has shown that ≥35 years of age at ART start was associated with virologic failure [OR=2.3] (21) and the Asia Pacific HIV Observational Database study found that lower CD4 cell count responses were found to be associated with increasing age (22). However, a prospective cohort study in South Africa found that treatment failure was higher in adolescents compared to young adults where incidence rate of treatment failure was 8.2 per 100 person years among adolescents (9-19 years) while it was 5.0 per 100 person years among young adults (20-28 years) (23). Similarly study conducted in Canada using retrospective data shown that viral rebound was independently associated with being younger in age (24)

Indian retrospective study found that patients from urban areas had 1.9 times greater hazard for treatment failure compared with those from rural areas (14).

A retrospective observational cohort study in rural South Africa, male gender (OR 1.7) significantly associated with treatment failure and immunologic failure (7, 25) . A study in India also show that men had a 3.5 times greater risk of treatment failure (14). However, these findings contradict with a study conducted in Canada (24).

Low education level was also found to be associated with immunologic failure (7).

Adherence

A study in Thailand found that virological failure was strongly associated with adherence of <95% (13), while in China <100% adherence was associated with virologic failure in 6-11 month follow up cohort (26). A study conducted in Uganda has also shown that poor adherence was associated with virologic failure [OR=3.9] (17). The risk of immunologic failure was 41% versus 19% among those with incomplete and complete adherence respectively after 48 months on ART (7). Adherence below 95% was strongly associated with immunological treatment failure (16).

CD4 count

A study in Thailand found baseline CD4 count <100cells/mm3 and slow CD4 cell recovery of <50cells/mm3 after 6 months of HAART to be predictors of immunological failure (13). A retrospective study at Massachusetts General Hospital has shown Treatment Failure was significantly associated with absolute neutrophil count <1000 cells/mm3 (HR= 2.90) and baseline CD4 count <200 cells/mm3 (HR = 1.90) (25).

In contrast higher mean CD4 cell counts were associated with lower baseline CD4 cell count and consistently undetectable viral loads (22, 27). Similarly, there was significant association between baseline CD4 of more than 100cell/ µl and immunological treatment failure in a study conducted in Tanzania (16).

Regimen

In a retrospective study, compared to other regimens, the percentage of treatment failure was significantly greater in the regimens that included efavirenz (14). In contrast a study conducted in Uganda patients treated with d4T/3TC/NVP were 2.6 times more likely to develop virologic failure than patients treated with ZDV/3TC/EFV (7). In contrast to this in a retrospective observational cohort study in rural South Africa, Zidovudine-use associated with treatment failure (27).

Patients who had negative changes in, hemoglobin concentration and body weight had 3.2 and 3.5 times significantly greater risk of treatment failure respectively than patients in whom there was a positive change (14).

There are studies conducted in different parts of the world to identify predictors of immunologic failure. But this information is scarce in Ethiopia especially no study has been conducted at Debremarkos Hospital. Hence, this study will fill this gap.

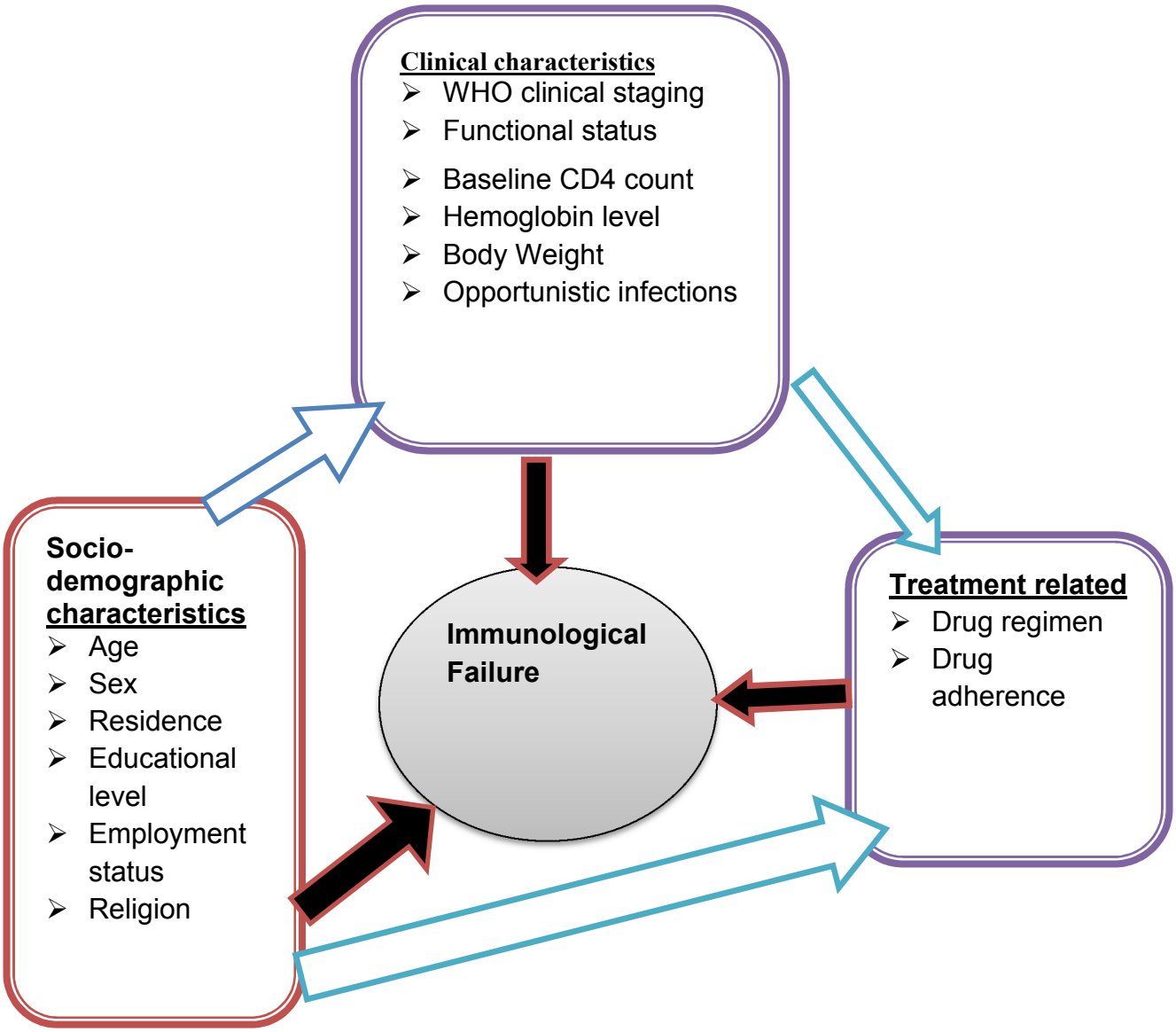

Fig 1: Conceptual framework of immunological failure and its predictors among HIV positive patients on ART.

1.3. JUSTIFICATION OF THE STUDY

Antiretroviral treatment failure will lead development of drug resistant virus unless it is detected early. This study will identify factors which will be used to predict immunological failure of treatment for the patient with those factors. If the time of failure is predicted the patient will get appropriate follow up and switched to second line ART without delay. Thus development of drug resistant virus which will occur due to keeping patients on failing regimen will be avoided.

In Ethiopia, patients on ART are monitored with immunological and clinical assessment, thus absence of viral load monitoring will let patients on failing regimen. By determining rate of immunological failure and identifying factors associated with it, the study will provide information for clinicians to use in the follow-up and management of patients on highly active antiretroviral treatment (HAART). Public health professionals will also use the findings in the design of ART related programs and care and support activities.

The study will also give baseline information for further studies that will be conducted on the problem in the study area and other similar settings.

2. OBJECTIVE

2.1. General Objective

- To assess rate of immunological failure and its predictors among patients on highly active antiretroviral treatment at Debremarkos Hospital, North West Ethiopia, 2012.

2.2. Specific Objectives

- To determine rate of immunological failure among patients on HAART at Debremarkos Hospital.
- To identify predictors of immunological failure among patients on HAART at Debremarkos Hospital.

3. METHODS

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3.1. STUDY DESIGN AND PERIOD

A retrospective longitudinal study was conducted in April 2012.

3.2. STUDY AREA

The study was conducted at Debremarkos Hospital which was established in 1964. The hospital is 300 km northwest of the capital Addis Ababa and 265 km southeast away from the Amhara regional city BahirDar. It serves for 3.5 million catchment population and has a total of 137 beds.

The free based ART service was started on September 30, 2005. Totally there are 8042 clients on HIV care service among these 4490 had ever started ART in the hospital. Currently there are 2611 clients taking their ART from the hospital.

3.3. POPULATION

3.3.1. **Source Population**

The target population for this study includes all patients age ≥ 15 years with HIV infection and had ever started antiretroviral treatment in Northwest Ethiopia.

3.3.2. **Study population**

All patients age ≥ 15 years with HIV infection and had ever started antiretroviral treatment at Debremarkos Hospital.

3.3.3. Inclusion and Exclusion Criteria

Inclusion criteria

All patients with documented HIV infection who were under medical care at the ART Clinic and met the following criteria were included:

- ≥ 15 years of age
- Started antiretroviral treatment within a period January 01, 2007 to April 01, 2008.
- Had at least six months of follow up and

Exclusion criteria

- Had missed baseline CD4 cell count and
- Had no at least one additional CD4 cell count after six month of ART follow up.

3.4. SAMPLE SIZE AND SAMPLING TECHNIQUE

Sample size was computed for determining rate of immunological failure and for identifying its predictors. Since there was no study conducted in Ethiopia on immunological failure studies from other African countries were used in sample size calculation.

Single population proportion formula was used to compute sample size for determination of rate of immunological failure. A study conducted in rural Uganda had shown that immunological failure was 7.9% at month 12 and 38% at month 24(17).

$$n = Z_{1-\alpha/2}^{2}[p(1-p)]/w^{2}$$

Assuming;

- a 0.05 level of significance,
- $Z_{1-\alpha/2}$ will be 1.96 and
- 0.05 margin of error, w, the minimum sample size was computed using each proportion.

Sample size for identifying predictors was also calculated by using the predictor variables from study conducted at the Chris Hani Baragwanath Hospital, in the Soweto town, South Africa (7) using EPI-INFO StatCalc software for cohort/comparative cross-sectional design. The following assumptions were considered for this calculation:

- Power = 85%
- Confidence level = 95%
- Ratio (number in exposed: non-exposed) = 1:1

Table 1: Sample size calculation with different proportions and predictors from two studies for determining rate and predictors of immunological failure at Debremarkos hospital, Northwest Ethiopia, 2012.

S.No.	Variable		Proportion			sample size
1	Immunological failure at					
		12 month	0.079			112
		24 month	0.38			362
		Assuming that proportion of Immunological failure at some point during follow up period	0.50			**384**
			P*exposed	P*unexposed	OR*	
2	**Education** No or primary education (exposed) Secondary or tertiary (unexposed)		8.0%	26.7%	0.34	218
3	**Adherence** <95%(exposed) 95-100(unexposed)		34.6%	18.1%	2.39	246

*P=proportion, OR=Odds Ratio

Accordingly, the minimum sample size was 384 and adding 10% for those patient charts with incomplete baseline variables the final sample size was 422.

There were 578 clients who started ART in the hospital within the period between January 01, 2007 and April 01, 2008 and fulfilled the inclusion and exclusion criteria. This time was chosen after assessment was conducted to find enough number of events and sample size.

Since it was logistically possible to include all 578 patients and good to increase the power of the study all 578 eligible patients were included in the study.

Thus, all 578 patients who had started ART at Debremarkos hospital within the period between January 01, 2007 and April 01, 2008 and fulfilled the inclusion criteria were taken to be followed until April 01, 2012 with maximum follow up of 5 years and 3 months.

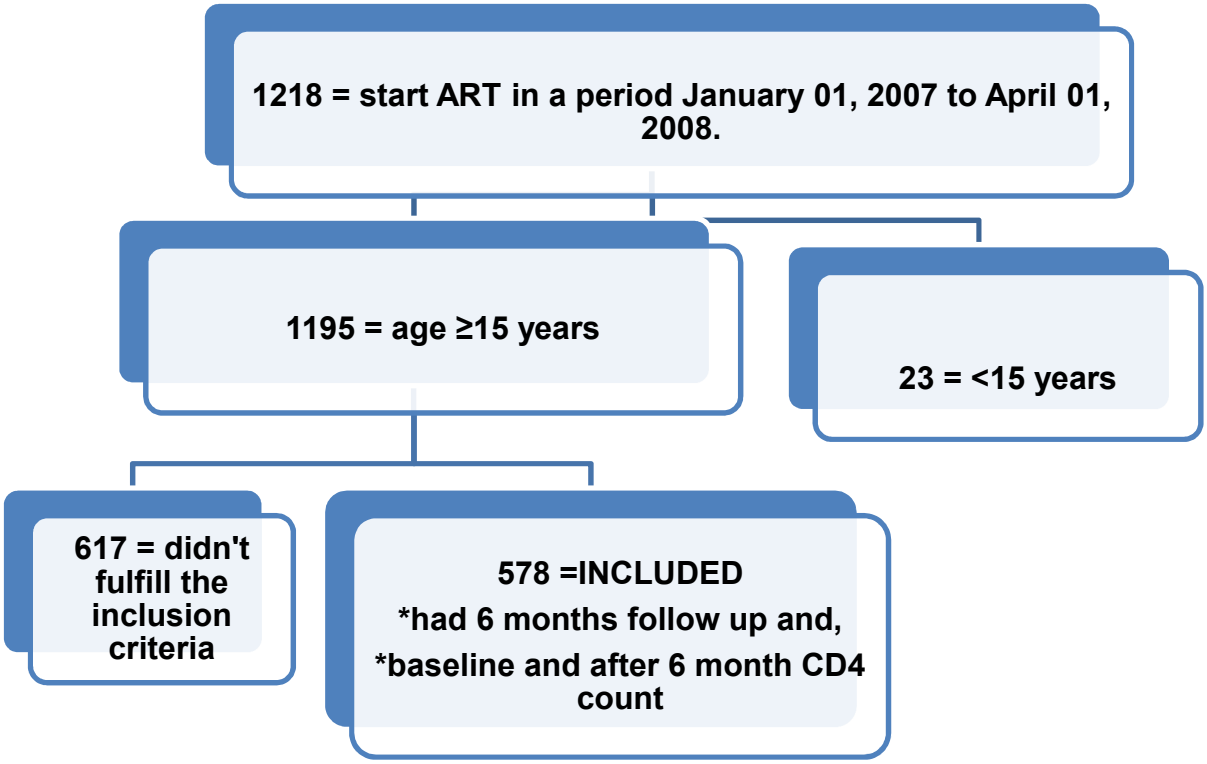


Fig. 2: Schematic presentation of sampling procedure from HIV/AIDS patients on ART at Debremarkos hospital, Northwest Ethiopia, May 2012.

3.5. VARIABLES OF THE STUDY

Dependent variable:

- Immunological failure and its time of occurrence

Independent variables:

- Socio-demographic variables
    - ✓ Age
    - ✓ Sex
    - ✓ Marital Status
    - ✓ Educational Status
    - ✓ Religion
    - ✓ Residence
- Base-line CD4 count
- WHO clinical stage at the baseline
- Functional status
- Type of regimens
- Drug Adherence
- Opportunistic infections at baseline
- Nutritional variables at baseline and changes during follow-up
    - ✓ hemoglobin
    - ✓ body weight

3.6. OPERATIONAL DEFINITIONS

- **Event:** Occurrence of immunological failure
- **Immunological Failure**: Immunological failure said to be occurred when there is:
    i. Fall of CD4 count to baseline (or below) OR
    ii. 50% fall from on-treatment peak value OR
    iii. Persistent CD4 levels below 100 cells/mm^3 (12).
- **Time to Immunological failure**: Time from initiation of ART up to occurrence of immunological failure.
- **Survival time:** The time a patient waits without immunological failure.
- **Censored:** Patients free of the event at the end of the study period or lost, died, transferred out or stop treatment before developing the event. For these patients, the data were censored at the date of the last visit.

3.7. DATA COLLECTION, QUALITY CONTROL AND ANALYSIS

3.7.1. **Data collection procedure**

Data were collected by three trained nurses. Data collection format was used to extract all the necessary information from patient's ART charts on the variables of interest. Pre-testing of the data collection format was done and modifications were made on it. The medical records of patients who had started ART in the period between January 01, 2007 and April 01, 2008 were followed from the date of enrollment to April 01, 2012 using data extraction format for the occurrence of the event.

The event was development of immunological failure. Immunological failure was said to be occurred when there is fall of CD4 count to baseline (or below) or 50% fall from on-treatment peak value or persistent CD4 levels below 100cells/mm^3. Patients free of the event at the end of the study period or lost, died, transferred out or stop treatment before developing the event were censored at the date of the last visit.

3.7.2. **Data Quality Control**

Pretesting was done on patient charts before the data collection was started to check the quality of the data extraction format and some modifications were made accordingly. One day training was given for three nurses who were working at the Art clinic of the hospital and daily supervision was done by the principal investigator. Completed data extraction formats were checked daily for their completeness.
Data entry and cleaning was done by the principal investigator.

3.7.3. **Data Analysis**

Data were first entered using Epi-Info 2002 and then analyzed using SPSS version 20. Descriptive statistics was used to describe the study subjects and different variables. Kaplan–Meier survival analyses were used to estimate the time from initiation of antiretroviral therapy to immunologic failure. Log rank test of equality of survival for the different categories of independent variables was also computed. Life table was computed to see the cumulative survival probability with six month time intervals. For patients who were not reached the endpoint, the data was censored at the date of the last visit. Bivariate and multivariate Cox-proportional hazard model was fitted to identify predictor variables of immunological failure. Variables with $P<0.2$ in a bivariate analysis were inserted into the multivariate analysis using Backward LR method. Hazard ratios and their 95% confidence intervals were computed. Variables with P-value of <0.05 were considered as significant predictors. The proportional hazards assumption was assessed with log-log plots and regression of the Schoenfeld residuals.

3.8. ETHICAL CONSIDERATION

Ethical clearance was obtained from the Institutional Ethical Review Board of Institute of Public Health, Gondar University. Permission letter was obtained from Debremarkos Hospital administration and ART coordinator. The names and ART unique numbers of patients were not used and confidentiality of information was kept by collecting data only by nurses who were working in the ART clinic.

4. RESULTS

4.1. Baseline Socio-Demographic Characteristics of the Study Participants

A total of 509 patients' records were included in the analysis giving 88.1% of complete information. Of which 302 (59.3%) were females. The median age of patients at the start of ART was 35 (IQR= 11) years. From all study participants 41.1% and 36.3% were in age the group of 25-34 and 35-44 (36.3%) years respectively.

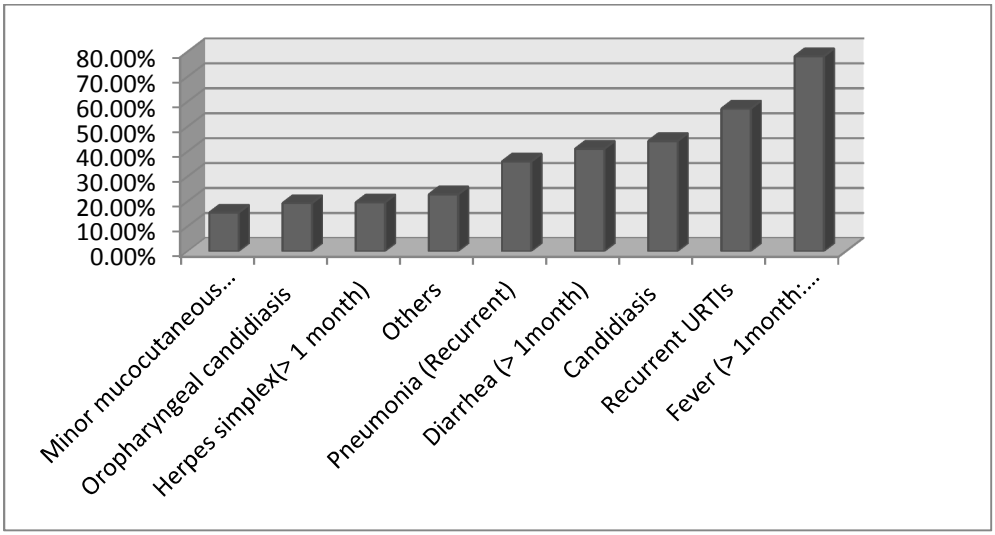
Most of patients 486 (95.5%) were Orthodox in their religion and married 200 (39.3%) in marital status. Concerning educational status, 36.5% of the study participants were with no education, 481(94.5%) had disclosed their HIV status.

Table 2: Baseline Socio-demographic characteristics of HIV/AIDS patients on antiretroviral therapy at Debremarkos Hospital, Northwest Ethiopia, May 2012.

Variables	Numbers	%
Sex		
Female	302	59.3
Male	207	40.7
Age (years)		
15-24	54	10.6
25-34	209	41.1
35-44	185	36.3
45-54	49	9.6
55+	12	2.4
Religion		
Orthodox	486	95.5
Muslim	18	3.5
Protestant	5	1.0
Employment		
Working full time	212	41.7
Unemployed	194	38.1
Not working due to ill health	57	11.2
Working part-time	46	9.0
Level of education		
no education	186	36.5
Primary	144	28.3
Secondary	136	26.7
Tertiary	43	8.4
Residence		
Urban	294	57.8
Rural	215	42.2

4.2. Clinical Characteristics of Patients at Initiation of ART

Almost all 493(96.9%) of patients had at least one opportunistic infection at the start of Antiretroviral therapy.



Others = CMV, Herpes zoster, toxoplasmosis (brain), Extra-pulmonary TB

Fig. 3: Past Opportunistic infection status of HIV/AIDS patients on antiretroviral therapy at Debremarkos hospital, Northwest Ethiopia, May 2012.

Two hundred seventy five (54.0%) patients were working in their functional status and 78.2% of patients were having Hemoglobin measurement of ≥10mg/dl at the start of ART. One hundred ninety five (38.3%) and 163 (32.0%) of patients had started treatment with Stavudine-Lamivudine- Nevirapine and Zidovudine-Lamivudine-Nevirapine regimen respectively.

Three hundred and eighteen (62.5%) of patients were eligible only by criteria of CD4 count less than 200 cells/mm^3 while 162(31.8%) were eligible by both CD4 bellow 200 and WHO stage II and III with total lymphocyte count (TLC) ≤1200. From the total patients included in the study about 212(41.6%) had CD4 count ≤100cells/mm^3 at antiretroviral initiation. The median baseline CD4 cell count was 117cells/mm^3 (IQR=99).

Table 3: Baseline Clinical characteristics of HIV/AIDS patients on antiretroviral therapy at Debremarkos Hospital, Northwest Ethiopia, May 2012.

Characteristics	Number	%
Eligibility criteria		
Only CD4 below 200	318	62.5
Both CD4 below 200 and WHO stage II and III with TLC≤1200	162	31.8
Both CD4 below 200 and WHO stage IV	22	4.3
WHO stage II and III with TLC<=1200	7	1.4
Functional status		
Working	275	54.4
Ambulatory	222	44.0
Bedridden	8	1.6
WHO clinical stage		
Stage I	1	0.2
Stage II	40	7.9
Stage III	451	88.8
Stage IV	16	3.1
Baseline CD4 count		
≤100 cell/mm^3	212	41.7
>100 cell/mm^3	297	58.3
Drug type at initiation		
d4t - 3TC- NVP	197	38.7
d4t - 3TC- EFV	97	19.1
AZT – 3TC- NVP	163	32.0
AZT – 3TC- EFV	52	10.2
Hemoglobin level		
<10mg/dl	70	15.0
≥10mg/dl	398	85.0

4.3. Immunological Failure after Initiation of Highly active Antiretroviral Treatment

Study participants were followed for a minimum of 6 months and maximum of 63 months with median time of 36 months (IQR: 12.00 - 49.50 months). A total of 107 (21%) patients found to have immunological failure after 63 months on ART. Based on the three criteria seated by WHO for defining immunological failure 62 (57.94%) were due to fall of CD4 counts to baseline or bellow while 44 (41.12%) were due to persistent CD4 counts bellow 100 cells/mm^3.

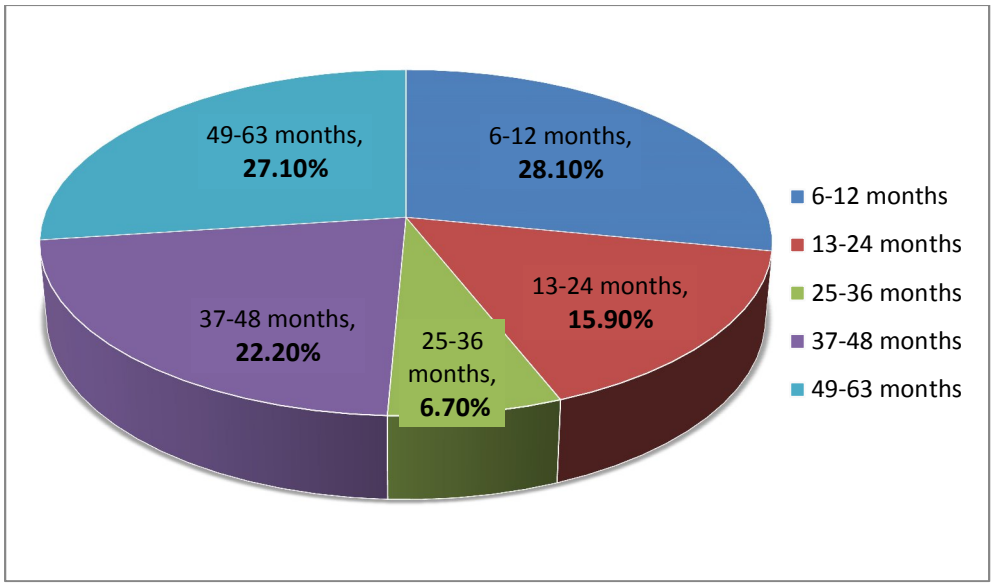


Fig. 4: Pie-chart for length of follow up time of patients on ART at Debremarkos hospital, Northwest Ethiopia, May 2012.

Among overall prevalence of immunological failure 33(6.5%) were failed at 6 month of follow up while 62(12.2%), 84(16.5%), 89(17.5%), 97(19.0%) were failed at 12, 18, 24 and 36 months of follow up respectively.

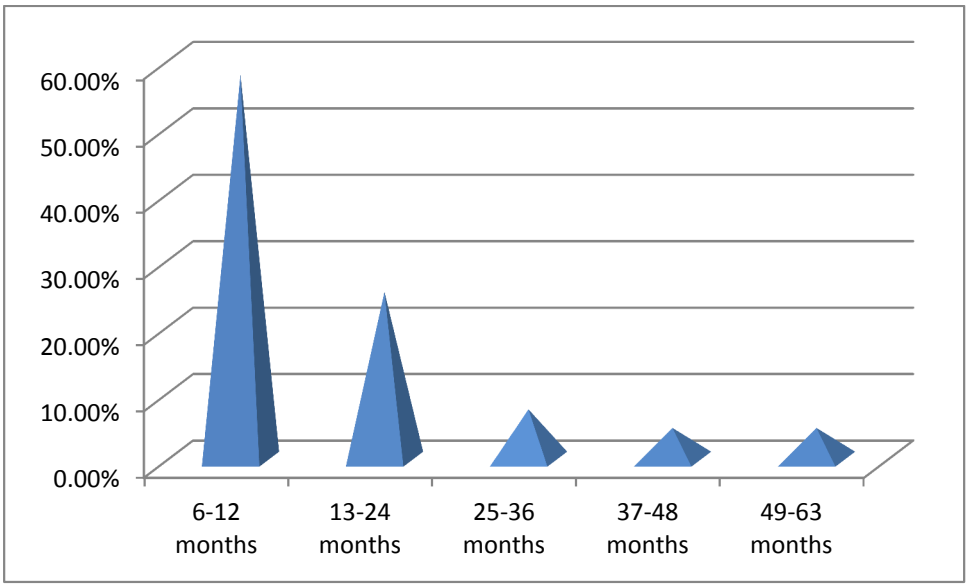


Fig. 5: Prevalence of immunological failure at different months of follow up of HIV/AIDS patients on antiretroviral therapy at Debremarkos hospital, Northwest Ethiopia, May 2012.

Participants were followed for different period of time and the total person-time of follow up was 1334.42 patient-years of follow up. The rate of immunological failure after 63 months on ART was 8 per 100 patient-years.

The remaining 402(79%) patients were censored for different reasons: alive without failure until the end of study period, transferred out, lost, dropout out, or died before the end of the study period without developing the event. The percent for each reasons of censoring did not represent the prevalence of each out come since the study didn't incorporate those with less than six months follow up on ART.

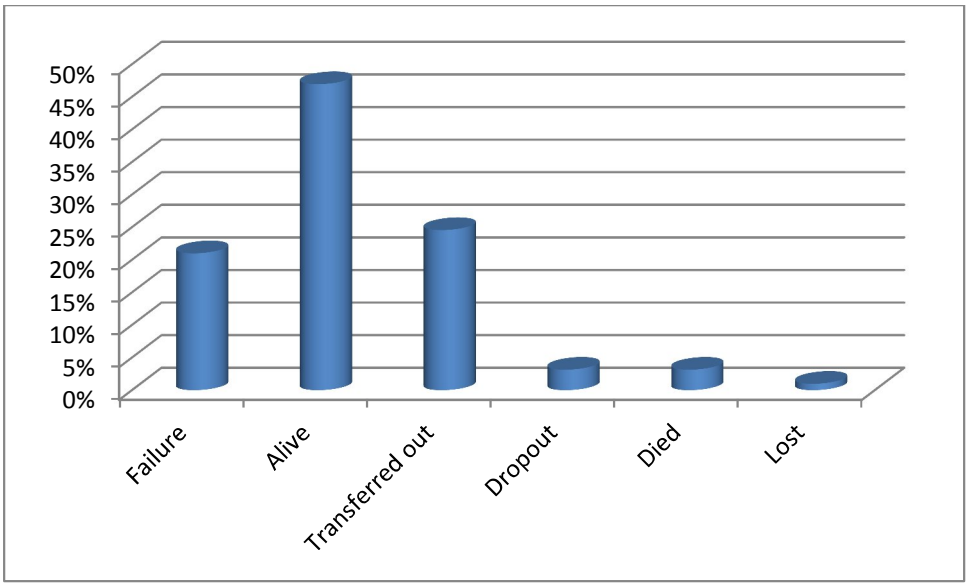


Fig. 6: Status of study participants at the last observation at Debremarkos hospital Northwest Ethiopia, May 2012.

The mean survival time was 51.045 (95%CI: 49.046, 53.043) months. Life table had shown the cumulative probability of survival at 6, 12, 24, 36 and 60 month was 0.88, 0.82, 0.79, 0.77 and 0.69 respectively.

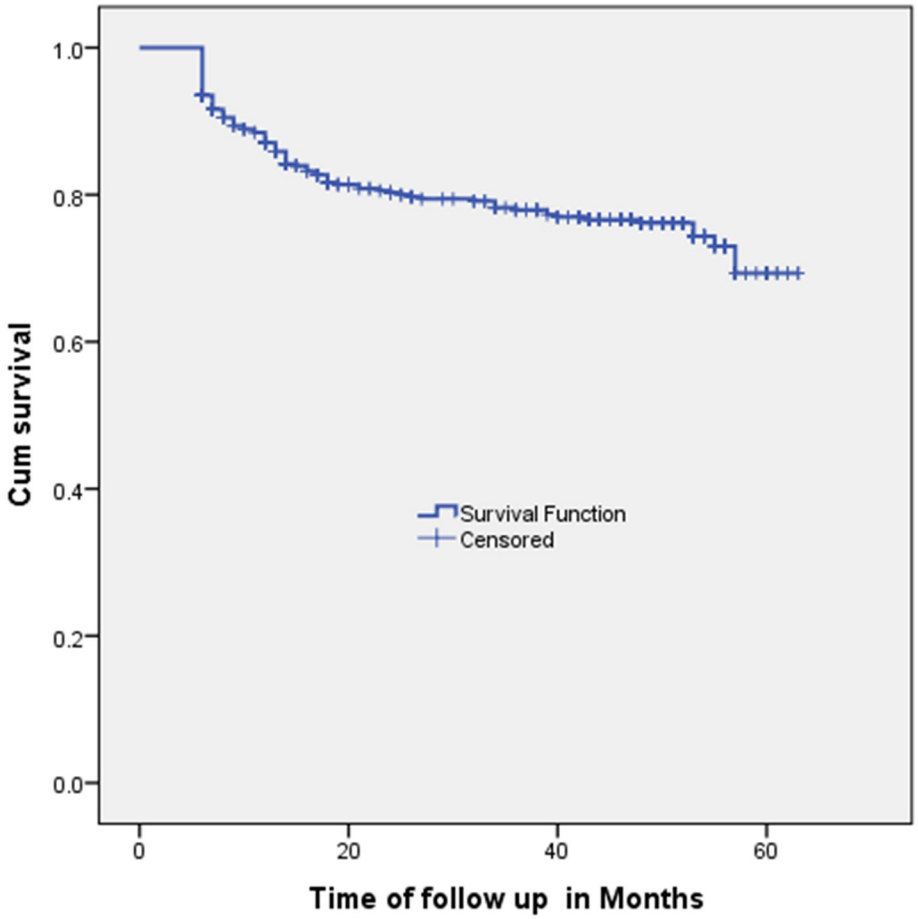


Fig. 7: Kaplan Meier curve for immunological failure of HIV infected patients taking antiretroviral therapy at Debremarkos hospital, Northwest Ethiopia, May 2012.

Fourty six (43.0%) and 41(38.3%) number of failure were seen in age group of 25-34 years and 35-44 years respectively. According to employment status 42(40.7%) of the failure were seen among unemployed patients while 27(26.2%) failures were among patients who were not working due to ill health.

Table 4: The outcome status of the study participants at the end of follow up with respect to baseline socio-demographic and clinical characteristics at Debremarkos Hospital, Northwest Ethiopia, May 2012.

Variables	Immunological Failure		Total
	Yes	No	
Age			
15-24	7(6.5%)	47(11.7%)	54(10.6%)
25-34	46(43.0%)	163(40.5%)	209(41.1%)
35-44	41(38.3%)	144(35.9%)	185(36.3%)
45+	13(12.2%)	48(11.9%)	61(12%)
Sex			
Male	53 (49.5%)	154 (38.3%)	207 (40.7%)
Female	54 (50.5%)	248(61.7%)	302 (59.3%)
Hemoglobin change*			
Positive change	8(33.3%)	10(14.7%)	18(19.6%)
No change /decrease	16(66.7%)	58(85.3%)	74(80.4%)
Weight change*			
Positive change	54(56.2%)	77(20.2%)	131(27.5%)
No change/decrease	42(43.8%)	304(79.8%)	346(72.5%)
Recurrent URTIs			
Yes	36(33.6%)	182(45.3%)	218(42.8%)
No	71(66.4%)	220(54.7%)	291(57.2%)
Baseline CD4			
≤100 cell/mm^3	63(58.9%)	149 (37.1%)	212(41.7%)
>100 cell/mm^3	44(41.1%)	253(62.9%)	297(58.3%)

*change = End value – initial value

4.4. Predictors of Immunological Failure

In Log rank test for the different categories of independent variables; Recurrent Upper Respiratory Tract Infections (URTIs), Employment, baseline CD4 cell count and Weight change were significantly associated with immunological failure.

Log rank test for the two levels of Recurrent URTIs had shown a chi-square value of 4.42 (p=0.036). Accordingly there is significant difference in failure time of patients with and without Recurrent URTIs.

Log rank test of equality of failure time distributions for the two levels of Weight change had shown a significant chi-square value of 48.908 (P<0.001). Patients that show increase in their body weight from the baseline to the last observation had significantly different failure time compared to patients that show no change or decrease in their body weight.

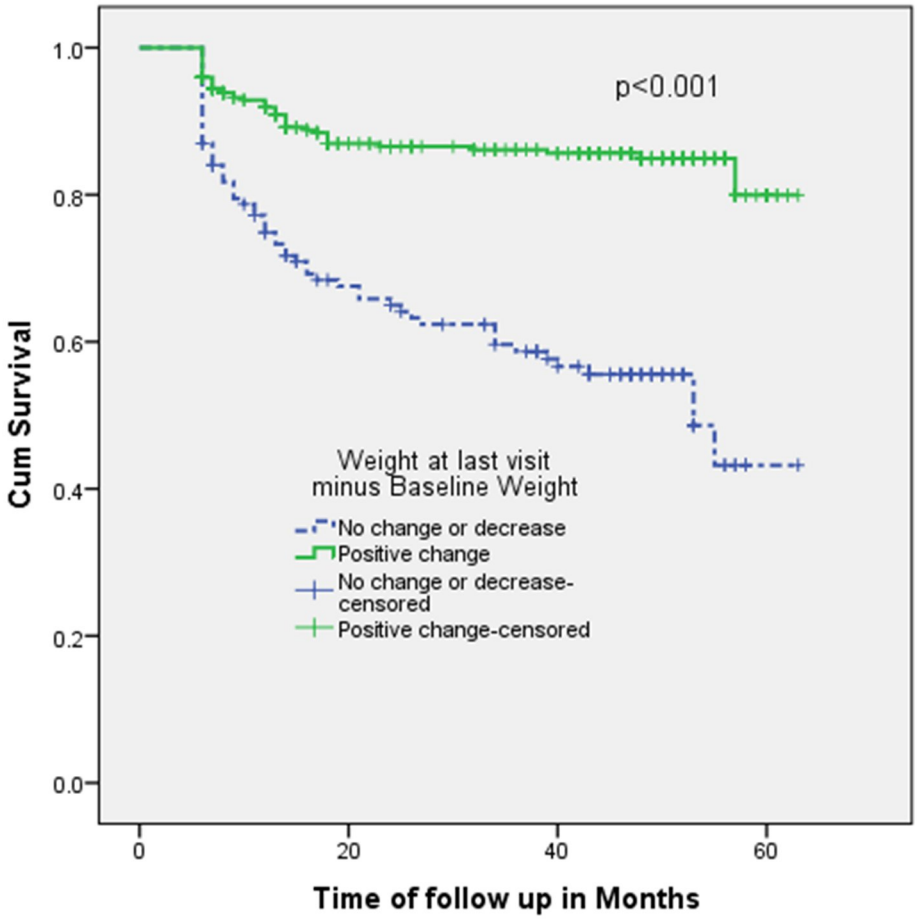


Fig. 8: Kaplan Meier curve comparing immunological failure of HIV patients on ART according to Weight change at Debremarkos hospital, Northwest Ethiopia, May 2012.

Log rank test for the two levels of baseline CD4 count had also shown significant difference in failure time between two levels of baseline CD4 counts with chi-square value of 16.902 (P<0.001). Therefore, there is a significant difference in failure time between patients with baseline CD4 ≤100cells/mm^3 and patients with baseline CD4 >100cells/mm^3.

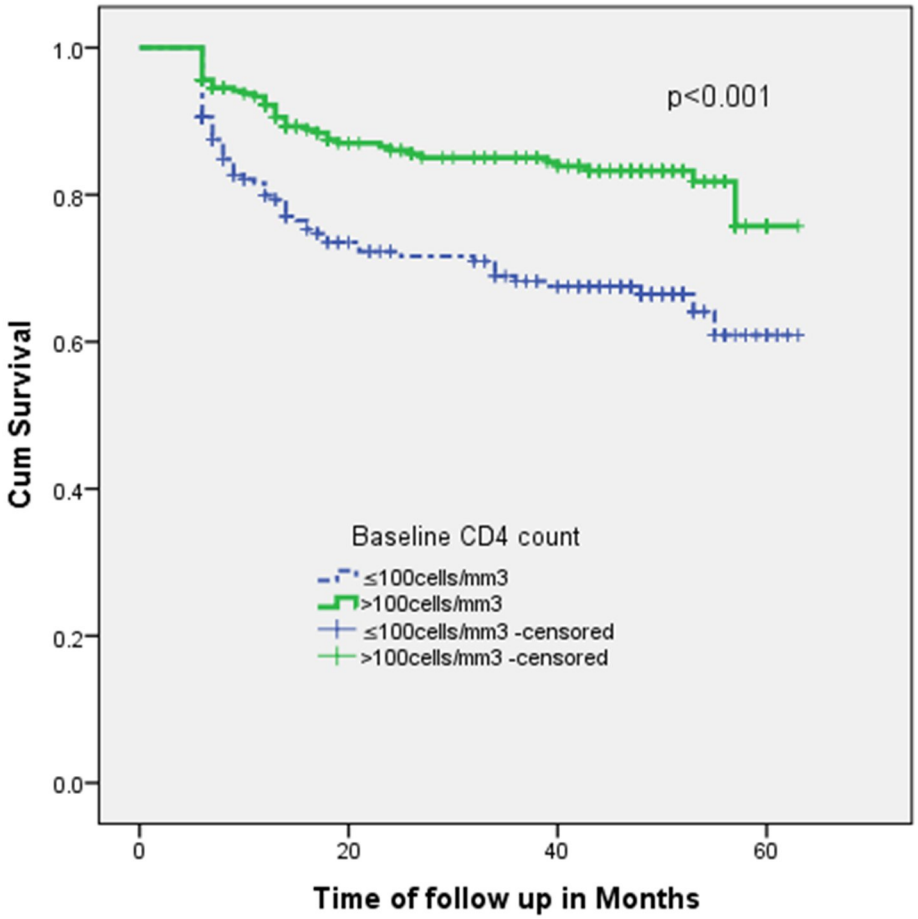


Fig. 9: Kaplan Meier curve comparing immunological failure of HIV patients on ART according to Baseline CD4 count category at Debremarkos hospital, Northwest Ethiopia, May 2012.

Log rank test for the different categories of employment had shown a chi-square value of 7.919 (p=0.048) which indicates that failure time was significantly associated with employment status.

Cox-Regression Analysis

The bivariate Cox-proportional hazard model was fitted for all explanatory variables and five variables; recurrent URTIs, employment, baseline CD4 count, and weight change were found to be significantly associated with time to immunological failure.

All explanatory variables with p-value of ≤0.2 were inserted in the multivariate Cox-regression to see the independent effect each variable on immunological failure. Sex, Recurrent URTIs, Pneumonia (recurrent), Employment, Baseline CD4 count and Weight change were the six explanatory variables fitted in the multivariate Cox-proportional hazard model with Backward LR method of analysis. Backward LR method was used to get the most parsimonious model by controlling multi co-linearity. The variables recurrent pneumonia infection, employment status, baseline CD4 count and weight change were found to be significantly associated with time to immunological failure in the multivariate analysis.

Accordingly, those patients with recurrent pneumonia infection at the baseline were 1.62 times at higher risk of immunological failure compared to those patients without recurrent pneumonia [AHR= 1.623, 95%CI: 1.095, 2.404].

Employment status was found to be significantly associated with immunological failure. Unemployed patients had 1.74 times higher hazard of immunological failure compared to those patients who were working full time [AHR= 1.741, 95%CI: 1.107, 2.738]. Similarly patients who were not working due to ill health had 2.19 times greater risk of immunological failure compared to full time worker patients at the start of ART [AHR= 2.19, 95%CI: 1.195, 4.015].

Baseline CD4 cell count was also significantly associated with immunological failure. Those patients with baseline CD4 count ≤100cells/mm^3 were 2.16 times more likely to have immunological failure at any time compared to those patients with CD4 count greater than 100cells/mm^3 [AHR= 2.160, 95%CI: 1.435, 3.252].

Weight change was also significant predictor of immunological failure. Accordingly those having had no change or decrease in their body weight had 4.34 times higher

hazard of immunological failure compared to those patients with positive change [AHR= 4.335, 95%CI: 2.930, 6.414].

Table 5: The Cox-Regression output for predictors of immunological failure among patients taking ART at Debremarkos Hospital, Northwest Ethiopia, May 2012.

Variable	Immunological Status		Crude HR [95% CI]	Adjusted HR [95% CI]
	Failed	Censored		
Recurrent Pneumonia				
Yes	63	263	1.39 [0.94, 2.04]	**1.62[1.09, 2.40]***
No	44	139	1	1
Recurrent URTIs				
Yes	36	182	1.52 [1.02, 2.28]*	
No	71	220	1	
Employment				
Working full time	32	180	1	1
Working part time	10	36	1.58[0.78, 3.21]	1.58[0.77, 3.23]
Not working due to ill health	17	40	2.12[1.18, 3.82]*	**2.19[1.20, 4.02]***
Unemployed	48	146	1.62[1.03, 2.53]*	**1.74[1.11, 2.74]***
Weight Change				
Positive	48	323	1	1
No/negative	59	79	3.53[2.41, 5.16]*	**4.34 [2.93, 3.23]***
Sex				
Male	53	154	1.19[0.98, 1.44]	
Female	54	248	1	
Baseline CD4				
≤100cells/m^3	63	149	2.18[1.48, 3.20]*	**2.16 [1.44, 3.25]***
>100cells/m^3	44	253	1	

*found significant at 0.05 level significance

5. DISCUSSION

Diagnosing treatment failure based on the clinical or immunological criteria will lead keeping patients on a failing regimen which in turn leads to the reversal of clinical conditions of patients to the pre-treatment state, increase risk of mortality and development of drug resistant strains. It will be shocking if once drug resistant virus start transmission in the population (10,11). This study was aimed at finding the predictors of immunological failure after start of first line antiretroviral drugs so that clinicians and other health care providers can predict the probability that a patient will develop immunological failure. This information will help in avoiding delay to switch the patient to second line regimen.

At the end of the 63 months follow up, 107 (21%) patients had developed immunological failure. This is higher than retrospective studies done in South Africa 13% (15) and Tanzania 17% (16) of immunological failure. This can be due to shorter follow up time of these two studies which were 48 and 29 months of follow up respectively. Similarly a retrospective cohort study with median follow up time of 44 months conducted Soweto, South Africa demonstrated an overall immunologic failure rate of 19% by month 99 (7) which was also lower even if the follow up time was longer than the current study which had a median follow up time of 36 months. This lower prevalence might be due to smaller sample size of 456 this study compared to 509 study subjects of the current study and socio-economic differences.

Among all prevalence of immunological failure 33(6.5%) were failed at 6 month of follow up while 62(12.2%), 84(16.5%), 89(17.5%), 97(19.0%) were failed at 12, 18, 24 and 36 months of follow up respectively. The result of this study underscore important feature of patients on ART that is high early immunological failure more than half of the 63 month prevalence were seen in the first 12 months follow up. This high early immunological failure might reflect the advanced stage of the disease at the start of the treatment due to different immunosuppressive opportunistic infections.

The rate of immunological failure after 63 months on ART was 8 per 100 patient-years of follow up. A systematic review conducted in in Africa found that failure rate per 100 patient years of follow-up was 2.64 in which failure was defined by using clinical/immunological definitions of treatment failure (19). This finding is much lower than the finding of the current study, this might be due to the reason that the current study uses only immunological criteria to define treatment failure. It might also be due to the socio-economic difference between those patients included in the systematic review and the current study subjects.

According to the multivariate Cox regression analysis patients with recurrent pneumonia infection at the initiation of ART were 1.62 times higher at risk of immunological failure compared to those patients without recurrent pneumonia keeping other variables constant. Thus it can be explained as those patients who suffer from recurrent pneumonia at the start of ART might be more immunosuppressed.

Employment status was also significantly associated with immunological failure. Accordingly, unemployed patients had 1.74 times higher risk of immunological failure compared to those patients who were working full time. Similarly patients who were not working due to ill health had 2.19 times greater risk of immunological failure compared to full time working patients at the start of ART. This might be due to the reason that those who work full time may have better income to get better care including diet than unemployed so that they will have better immunological response. Those patients unable to work due to ill health were also at higher risk of immunological failure compared to working patients, this can be due to the reason that not working patients were at advanced stage of the disease and greater immunosuppression and also can be due to loss of income due to being unable to work. So that, not working patients may have poor immunological response.

Baseline CD4 cell count was the other variable which had shown a significant association with immunological failure. Those patients with baseline CD4 count ≤100cells/mm^3 were 2.16 times more likely to have immunological failure at any time compared to those patients with baseline CD4 count greater than 100cells/mm^3. This association was also seen in a study conducted in Thailand which also found

low baseline CD4 as predictor of immunological failure (13). Similarly in a retrospective study conducted in South Africa found that patients initiating ART with a CD4 cell count of >100 cells/ml had a significantly higher median CD4 cell count in comparison to patients started on ART at a CD4 cell count of ≤100 cells/ml throughout the follow-up period (7).

This can be due to the reason that patients with lower baseline CD4 count are more immunosuppressed than those patients with higher CD4 count so that they will fail to have increased CD4 response while patients with ≥100cells/mm^3 are better to have increased CD4 response on treatment follow up. Lower baseline CD4 count indicates more advanced stage of HIV/AIDS.

In contrast a study done in Tanzania found that immunological failure was significantly associated with baseline CD4 count of more than 100cells/µl (16). This might be explained as those patients with higher baseline CD4 might have higher probability to be failed by the criteria of fall CD4 count to baseline or bellow even if that failing count might be higher than those patients with low baseline CD4.

Weight change also had shown strong association with immunological failure. Accordingly, those patients having had no change or decrease in their last body weight from the baseline had 4.34 times higher hazard of immunological failure compared to those patients with positive change. This finding was similar to the finding of a study done in India in which patients who had negative changes in body weight had 3.5 times significantly greater risk of immunological failure than patients in whom there was a positive change (14). This can be explained as, an increase in body weight may indicate better diet and better health this in turn may be due to improvement of immunity including increase in CD4 cells.

Drug adherence was not significant predictor of immunological failure in the current study while poor adherence was found to be significant predictor of treatment failure in other studies(7, 17). This might be due to the reason that adherence was measured only by patients self-report in our study. Mostly patients tell what the care giver desire, so they report as they were good adherents.

Hemoglobin measurement was not used in the analysis because of high number of missing values. This might be due to the reason that clinicians and care givers may

not take it as an important for following and managing patients. But in a study conducted in India found that patients who had negative changes in hemoglobin concentration had 3.2 times greater risk of immunological failure than patients in whom there was a positive change (14).

6. LIMITATIONS

Being retrospective limits the study to find out more predictors than those recorded in the charts.

Data incompleteness especially for follow up variables was also the other limitation which made difficulty to see clinical responses of patients since the data was collected from secondary source.

The other limitation of this study was that since failure was only measured by immunological criteria it may not assure the presence of treatment failure.

There were patients who were on follow up but had no CD4 count for more than 6 month gap from previous count. Misclassification bias might be occurred in these patients who had missed the CD4 measurement on time.

7. CONCLUSIONS

- The immunological failure rate was higher compared with other studies conducted in sub-Sahara African countries.
- There was high early immunological failure, more than half of immunological failures occurred during the first 12 months of ART initiation.
- The independent predictors of immunological failure were; having had recurrent pneumonia infection, being unemployed, being unable to work due to ill health, low baseline CD4 count and no change or decrease in body weight.

8. RECOMMENDATIONS

To Hospitals and Health care providers managing Patients on ART

- Viral load monitoring for patients who are at higher risk of immunological failure not to let them on a failing regimen.
- Continue follow up of patients with regular body weight measurement to early detect treatment failure.
- Shall improve regular hemoglobin measurement and recording.
- Strengthening and continuing in informing patients about the need for early diagnosis of HIV infection and timely start of ART before further immunosuppression had occurred. Since it is important to decrease the risk of immunological failure.

To governmental and non-governmental organizations

- Shall strengthen and continue in finding strategy to help and support unemployed patients in increasing their income.

To researchers

- Further Studies with prospective follow up design shall be planned to find out additional predictors of immunological failure.
- Recurrent pneumonia was found to be independent predictor of immunological failure; this finding needs more study on pathophysiology recurrent pneumonia and its association with lower CD4 response.

9. REFERENCES

1. WHO. Regional HIV and AIDS statistics, 2010 and 2001Accessed on 23/02/2012 Available from: http://www.etharc.org/resources/download/view.download/31/607.
2. USAID. HIV/AIDS HEALTH PROFILE: Sub-Saharan Africa, March 2011 Accessed on 18/02/2012 Available from: http://www.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf.
3. AAHAPCO. Addis Ababa HIV/AIDS Prevention & Control Office. 2012 [Accessed on 23/02/2012]; Available from: http://aahapco.org/.
4. Global, Health, Council. HIV/AIDS, Testing and counselingAccessed on 23/02/2012. Available from: http://www.globalhealth.org/view_top.php3?id=815.
5. MOH, FHAPCO. Update as of end of Tir 2002 (February, 2010) Monthly HIV Care and ART Update. Accessed on 15/02/2012. Available from: http://www.etharc.org/resources/download/view.download/42/347,.
6. Boyd M. Current and future management of treatment failure in low- and middle-income countries. . Current Opinion on HIV AIDS. 2010;5(1):83-9.
7. El-Khatib Z, Katzenstein D, Marrone G, Laher F, Mohapi L, Max, et al. Adherence to Drug-Refill Is a Useful Early Warning Indicator of Virologic and Immunologic Failure among HIV Patients on First-Line ART in South Africa. PLoS ONE. 2011;6(3).
8. Keiser O, MacPhail P, Boulle A, Wood R, Schechter M, Dabis Fo, et al. Accuracy of WHO CD4 cell count criteria for virological failure of antiretroviral therapy. Tropical Medicine and International Health. 2009;14(10):1220–5.
9. WHO, HIV/AIDS, Programme. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for public health approach. 2006 revisionAccessed on 20/02/2012 Available from: http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
10. Petersen ML, Laan MJvd, Napravnik S, Eron JJ, Moore RD, Deeks SG. Long term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. AIDS. 2008;22(16):2097–106.
11. Mutevedzi PC, Lessells RJ, Rodger AJ, Newell M-L. Association of Age with Mortality and Virological and Immunological Response to Antiretroviral Therapy in Rural South African Adults. PLoS ONE. 2011;6(7).
12. WHO. Antiretroviral therapy for HIV infection in adults and adolescents Recommendations for a public health approach 2010 revision. Accessed on 20/02/2012 Available from: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf
13. Khienprasit N, Chaiwarith R, Sirisanthana T, Supparatpinyo K. Incidence and risk factors of antiretroviral treatment failure in treatment-naïve HIV-infected patients at Chiang Mai University Hospital, Thailand AIDS Research and Therapy. 2011;8(42).
14. Rajasekarana S, Jeyaseelanb L, Vijilaa S, Gomathia C, Raja K. Predictors of failure of first-line antiretroviral therapy in HIV-infected adults: Indian experience. AIDS. 2007;21(4):47-53.
15. Barth RE, Tempelman HA, Moraba R, Hoepelman AIM. Long-Term Outcome of an HIV-Treatment Programme in Rural Africa: Viral Suppression despite Early Mortality. . AIDS Research and Treatment 2011.
16. Jaka HM, Mshana SE, Liwa AC, Peck R, Kalluvya S. Prevalence of immunological failure and durability of first line antiretroviral therapy at Bugando Hospital Mwanza, Tanzania. Tanzania Medical Journal. 2009;24(2).
17. Ahoua L, Guenther G, Pinoges L, Anguzu P, Marie-, Chaix L, et al. Risk factors for virological failure and sub-therapeutic antiretroviral drug concentrations in HIV-positive adults treated in rural northwestern Uganda. BMC Infectious Diseases. 2009;9(81).

18. Ekouevi DK, Coffie PA, Chaix M-L, Tonwe-Gold B, Amani-Bosse C, Leroy V, et al. Immunological response to highly active antiretroviral therapy following treatment for prevention of mother to child transmission of HIV-1: a study in Côte d'Ivoire. Journal of the International AIDS Society. 2010;13(28).
19. Renaud-Théry F, Duncombe C, Kerr S, Thierry S, Perriëns J. Adult antiretroviral therapy in resource limited settings: a systematic review of first-line failure and attrition rates2003-2008 26/05/2012. Available from: http://www.who.int/entity/hiv/topics/treatment/First_Line_ART_failure_RLS_metanalysis.pdf.
20. Assefa Y, Kiflie A, Tesfaye D, Mariam DH, Kloos H, Edwin W, et al. Outcomes of antiretroviral treatment program in Ethiopia: Retention of patients in care is a major challenge and varies across health facilities. BMC Health Services Research. 2011;11(81).
21. Kiguba R, Byakika-Tusiime J, Karamagi C, Ssali F, Mugyenyi P, Katabira E. Discontinuation and Modification of Highly Active Antiretroviral Therapy in HIV-Infected Ugandans Prevalence and Associated Factors J Acquir Immune Defic Syndr. 2007;45(218-223).
22. Egger S, Petoumenos K, Kamarulzaman A, Hoy J, Sungkanuparph S, Chuah J, et al. Long-Term Patterns in CD4 Response Are Determined by an Interaction Between Baseline CD4 Cell Count, Viral Load, and Time: The Asia Pacific HIV Observational Database (APHOD). . J Acquir Immune Defic Syndr. 2009;50(513-520).
23. Nglazi MD, Kranzer K, Holele P, Kaplan R, Mark D, Jaspan H, et al. Treatment outcomes in HIV-infected adolescents attending a community-based antiretroviral therapy clinic in South Africa. BMC Infectious Diseases. 2012;12(21).
24. Lima VD, Bangsberg DR, Harrigan PR, Deeks SG, Yip B, Hogg RS, et al. Risk of Viral Failure Declines with Duration of Suppression on HAART, Irrespective of Adherence Level. Acquir Immune Defic Syndr. 2010 55(4):460-5.
25. Robbins GK, Daniels B, Hui Zheng P, Chueh H, Meigs JB, Kenneth A. Freedberg. Predictors of Antiretroviral Treatment Failure in an Urban HIV Clinic. J Acquir Immune Defic Syndr. 2007;44(1):30-7.
26. Ma Y, Zhao D, Yu L, Bulterys M, Robinson ML, Zhaoa Y, et al. Predictors of virologic failure in HIV-1-infected adults on first line antiretroviral therapy in eight provinces in China. Clinical Infectious Disease. 2010; 50 (2):264–71.
27. Kantor R, Diero L, DeLong A, Kamle L, Muyonga S, Mambo F, et al. Misclassification of First-Line Antiretroviral Treatment Failure Based on Immunological Monitoring of HIV Infection in Resource-Limited Settings Clinical Infectious Diseases. 2009;49:454-62.

ANNEX

Annex 1: Data Collection Format

Data Extraction Format

This questionnaire is prepared for the collection of socio-demographic, clinical, treatment and immunological related information that are important for the assessment of immunological failure and associated factors. All this information will be retrieved from the clients ART and pre-ART registration book/chart without mentioning the name of client. This information will be collected by the nurses who are currently working in the ART clinic of the Debremarkos hospital.

Contact Information

1. Yayehirad Alemu (Principal Investigator) Tel: +251-913-250804
2. Ato Tadesse Awoke (Advisor) Tel: +251-910-173308
3. Ato Mamo Wubshet (Advisor) Tel: +251-912-180307

Part I: Socio-demographic Characteristics

Circle the letter of choice and say Data Not Available (DNA) when there was missed data.

ART Unique ID No.: _____ patient Card No.:_____

s.no.	Variable	Description/category
1	Age (years) at initiation	
	Sex	1. Male 2. Female
2	Marital-Status	1. Never married 4. Divorced 2. Married 5. Widowed 3. Separated
3	Level of Education	1. No education 2. Primary 4. Secondary 5. Tertiary
4	Patient address	1. Woreda _____ 2. Kebele _____
5	Religion	1. Muslim 3. Catholic 2. Orthodox 4. Protestant 5.other _____
6	Employment	1. Working full time 3. Not working 2. Working part-time 4. Unemployed
7	Disclosure status	1. Disclosed 2. Not disclosed
8	Addictions (Substance abuse)	1. Tobacco 3.Soft drugs 2. Alcohol 4. Hard drugs

Part II: Antiretroviral Treatment

s.no.	Variable	Description/category
1	past Opportunistic Illness	1. Candidiasis 2. Oropharyngeal candidiasis 3. Diarrhea (>1 month) 4. Kaposi Sarcoma 5. Recurrent pneumonia 6. Pneumocystis Carinii pneumonia 7. Toxoplasmosis 8. Others/specify_____
2	OI prophylaxis	1. Cotrimoozole 2. INH 3. Fluconazol 4. None
3	Eligibility criteria	1. Immunological/CD4 below 200 2. WHO stage IV 3. Both
4	Date ART started	_____/_____/_____ (E.C)
5	Regimen	1. 1a(30) =d4t (30) - 3TC - NVP 2. 1a(40) =d4t (40) - 3TC - NVP 3. 1b(30) =d4t (30)- 3TC- EFV 4. 1b(40) =d4t (40)- 3TC- EFV 5. 1c = AZT-3TC-NVP 6. 1d = AZT-3TC-EFV

Part III: follow up values of selected criteria

Follow up date (dd/mm/yy)	Months on ART	CD4/mm^3	WHO stage (1-4)	Functional status (W,A,B)	TB screen (P/N)	OIs	ARV drug Adherence (G,F,P)	Hgb(mg/dl)	Weight(kg)

Patient's status at last visit

1. **Date of last visit** _____/_____/_____ (E.C)
2. **Status**
    1. Alive
    2. Dropout
    3. Transferred out
    4. Died

Questionnaire filled and completed by

Name _____

Signature _____

Date_____

Approved by

Name _____

Signature _____

Date_____

Annex 2- Information Sheet

Title of the Research Project: Immunological Failure and Associated Factors among patients on antiretroviral treatment at Debremarkos Hospital, North West Ethiopia.

Name of Principal Investigator: Yayehirad Alemu
Name of the Organization: University of Gondar, College Of Medicine and Health Sciences.
Name of the Sponsor: University of Gondar
Introduction: This information sheet is prepared for Debremarkos Hospital administration and hospital ART program coordinating office. The aim of the form is to make the above concerned offices clear about the purpose of research work, data collection procedures and get permission to undertake the research.
Purpose of the Research Project: To assess antiretroviral treatment failure and associated factors in patients taking ART at Debremarkos Hospital, North West Ethiopia.

Procedure: In order to achieve the above objective, sample of patients will be taken from all HIV infected adults and who are on ART in the hospital.

Risk and /or Discomfort: By participating in this research project, there is totally no risk that comes to one whom document is reviewed whereas the review is of great importance to the research project; which is in turn important for overall planning of the ART program.
Benefits: The research have no direct benefit for one whose document/record is included in this research. But the indirect benefit of the research for the participant and all other clients in the program is clear. This is because if program planners prepare plan for the program based on the result of this study clients in the program will benefit by getting appropriate care and treatment services.
Of all, the research work has a paramount direct benefit for health care planners and managers, especially for those on ART program planning and management.

Confidentiality: To keep the confidentiality of the records of the clients, the record will be extracted by ART clinic staff nurses. Then, nurse data collectors will review the selected charts. The information collected from this research project will be kept strictly confidential and information reviewed about the clients by this study will be stored in a file, without name i.e. investigator uses number codes to the record during the review. The information gathered will not be accessible to anyone except the principal investigator and will be kept locked with password and appropriate locks.

Person to contact: This research project will be reviewed and approved by the institutional review board of college of medicine and health sciences, University of Gondar. If in case you want to know more information about the research and its undertakings, you can contact the committee through the address of the advisor and/or the principal investigator below.

1. Ato Tadesse Awoke (BSc Statistics, MSc Biostatistics), University of Gondar, college of medicine and health sciences, Institute of public health: Advisor
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2. Ato Mamo Wubshet (MSc., PhD candidate): Gondar University, college of medicine and health sciences, Institute of public health: Advisor
   Tel: +251-912-180307 e-mail: Mamo_wubshet@yahoo.com

3. Yayehirad Alemu: Gondar University, College of Medicine and Health Science, Institute of Public Health: Principal Investigator
   Cell phone: +251- 09 13 25 08 04 E-mail: 078yayu@gmail.com

Permission: You are kindly requested to permit and forward your permission to concerned body in your organization so that the researchers can get cooperation from the data clerks and other responsible bodies in place.

የመረጃና የስምምነት ውል ቅፅ

የምርምሩ/ጥናቱ ርዕስ:-

በደበረማረቆስ ሆስፒታል የፀረ-ኤች አይ ቪ መድሃኒት የሚጠቀሙ አዋቂዎች መድሃኒት መዉሰድ ከጀመሩ በኋላ የሚፈጠረዉን የህክምና አለመሳካት እና ተዛመጅ ምክንያቶችን በተመለከተ ::

የዋና ተመራማሪው ስም፡ ያየህራድ ዓለሙ

የድርጅቱ ስም: በጎንደር ዩኒቨርሲቲ ህክምናና ጤና ሳይንስ ኮሌጅ የህብረተሰብ ጤና አጠባበቅ ኢነስቲቲዩት

ወጪውን የሚሸፍነው አካል፡ ጎንደር ዩኒቨርሲቲ

መግቢያ:

ይህ የመረጃና የስምምነት ውል ቅፅ የተዘጋጀው ለ ደበረማረቆስ ሆስፒታል አስተዳደር አንዲሁም በሆስፒታሉ ለሚገኘዉ የፀረ-ኤች አይ ቪ ህክምና አሰተባባሪ ነዉ:: ዋና ዓላማዉም ስለ ምርምሩ ዓላማ፣ ስለ መረጃ አሰባሰቡ እንዲሁም ጥናቱን ለማካሄድ ፈቃድ ለማግኘት ከላይ የተገለፁትን አካላት ግልፅ እንዲሆንላቸዉ ለማድረግ ነዉ::

የጥናት ፕሮጀክቱ የሚካሄድበት ምክንያት :

የጥናቱ ዓላማ በ ደበረማረቆስ ሆስፒታል የፀረ-ኤች አይ ቪ መድሃኒት የሚጠቀሙ አዋቂዎች መድሃኒት መዉሰድ ከጀመሩ በኋላ የሚፈጠረዉን የህክምና አለመሳካት እና ተዛመጅ ምክንያቶችን ለማጥናት ታቅዶ የተዘጋጀ ነዉ :: የጥናቱ ግኝት ችግሩን ለመፍታ በተለይም ደግሞ ጥናቱ በሚካሄድበት ቦታ ትክክለኛ የሆነ የመፍትሄ አቅጣጫ ለመቅረፅ እንደመነሻ መሠረት ያገለግላል::

አተገባበር:

የጥናቱን አላማ ለማሳከት በ ደበረማረቆስ ሆስፒታል የፀረ-ኤች አይ ቪ መድሃኒት ከሚጠቀሙ አዋቂዎች ናሙና ይዎስዳል:: መረጃዉም የሚሰበሰበዉ ሙሉ በሙሉ በቻርት ላይ የተመሰረተ ነዉ::

ሊገጥም የሚችል ችግር/አለመመቸት

በዚህ ጥናት ላይ ቻርታቸዉ የሚታይባቸዉ አዋቂዎች ምንም የሚደርስባቸዉ ጉዳት የለም:: ነገር ግን መረጃቸዉ ለጥናቱ በጣም አስፈላጊ ነዉ::

ጥቅሞች:

በዚህ ጥናት ተሳታፊ የሚሆኑት የፀረ-ኤች አይ ቪ ህክምና ተከታታዮች በቀጥታ ሊያገኙት የሚችሉት ጥቅም ባይኖርም መረጃቸዉ ግን የፀረ-ኤች አይ ቪ መድሃኒት የሚጠቀሙ ህፃናት መድሃኒት ከጀመሩ በኋላ ያላቸዉን የህክምና ክትትል

አለመሳካት እንዲሁም ተዛመጅ ክንያቶችን ለማጥናት ይጠቅማል፡፡ ቀጥተኛ ባልሆነ መልኩም ቢሆን የፀረ-ኤች አይ ቪ ህክምና ተከታታዮች ተጠቃሚ ይሆናሉ፡፡

ምስጢራዊነት:

ለዚህ ጥናት የሚሰበሰበውን መረጃ ምስጢር ለመጠበቅ ሲባል መረጃዉ የሚሰበሰበዉ በሆስፒታሉ ዉስጥ በሚገኘዉ የፀረ-ኤች አይ ቪ መድሃኒት መስጫ ክሊኒክ በሚሰሩ ነርሶች ነዉ፡፡ ከዚያ በኃላ የተመረጡት ነርሶች የፀረ-ኤች አይ ቪ ህክምና ተከታታዮች ቻርት ላይ የሚገኘዉን መረጃ በሙሉ ይሰበስባሉ፡፡ የተሰበሰበዉ መረጃም ከጥናቱ ዋና ተመራማሪ እና ረዳቶቹ በስተቀር ለሌላ ለማንኛዉም አይነት ሰዉ ግልፅ አይሆንም፡፡

ሊገኙዋቸዉ የሚችሉ ሰዎች

ይህ የምርምር ፕሮጀክት በጎንደር ዩኒቨርስቲ የስነ ምግባር ኮሚቴ ተከልሶ የሚፀድቅ ይሆናል፡፡ የበለጠ መረጃ ማግኘት የሚፈልጉ ከሆነ ኮሚቴዉን በሚከተሉት አድራሻ ማግኘት የችላሉ፡፡ የትኛዉም ዓይነት ጥያቄ ቢኖርዎት ከዘህ ቀጥሎ የተጠቀሱትን ግለሰቦች ማግኘትና በማንኛዉም ጊዜ መጠየቅ የችላሉ፡፡

1. አቶ ታደሰ አወቀ :-ጎንደር ዩኒቨርስቲ፣ የህክምናና ጤና ሳይንስ ኮሌጅ፣ የህብረተሰብ ጤና አጠባበቅ ኢንስቲቲዩት፣ የጥናቱ አማካሪ

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Declaration

I, the undersigned, senior MPH student declare that this thesis is my original work in partial fulfillment of the requirement for the degree of Master of Public Health in Epidemiology and Biostatistics.

Name: _____

Signature: _____

Place of submission: Institute of public Health, College of Medicine and Health Sciences, University of Gondar.

Date of Submission: _____

This thesis work has been submitted for examination with our approval as university advisor(s).

Advisors

	Name	Signature	Date
1.	Ato Tadesse Awoke	_____	_____
2.	Ato Mamo Wubshet	_____	_____

ASSURANCE OF INVESTIGATOR

I, the undersigned, senior MPH student agree to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as pre terms and conditions of the research and publications office of the University of Gondar.

Name of the student: _____

Date: _____ Signature: _____

Approval of the advisor (s)

Advisors

Name	Signature	Date
1. Ato Tadesse Awoke	_____	_____
2. Ato Mamo Wubshet	_____	_____